Thorax, 1980, **35**, 581–585

Bronchial disease in ulcerative colitis

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ABSTRACT Ten patients with ulcerative colitis, all of whom were non-smokers, presented with a productive cough. In six, the chest radiograph was normal and cough was the only symptom; three of these patients had a minor obstructive ventilatory defect on testing. Four patients complained of exertional dyspnoea and had both an abnormal chest radiograph with bilateral pulmonary shadows and a mixed obstructive and restrictive ventilatory defect. Bronchial epithelial biopsies from four patients (two with and two without pulmonary shadows) revealed basal reserve cell hyperplasia, basement membrane thickening, and submucosal inflammation, changes more usually associated with cigarette smoking. Inhaled beclomethasone diproprionate relieved cough in seven patients. The occurrence of airway epithelial disease in association with ulcerative colitis raises the possibility of a systemic mechanism affecting both bronchial and colonic epithelium. It does not seem likely that sulphasalazine was the cause of the pulmonary syndrome in these subjects.

Inflammatory bowel disease, especially ulcerative colitis, is well recognised to be associated with systemic complications. Until recently, the lungs have been considered free from involvement, although there have been reports of patients with alveolitis attributed to sulphasalazine therapy.[1 2] Wegner's granulomatosis and pulmonary vasculitis have been described in patients with ulcerative colitis as has a suppurative bronchitis and bronchiectasis, and these syndromes seem unrelated to therapy.[3-6] In the present study, 10 patients with ulcerative colitis referred for pulmonary assessment are reported. Four were found to have a previously unreported bronchial epithelial abnormality and seven responded symptomatically to inhaled beclomethasone diproprionate.

Methods

Ten patients, three men and seven women, in whom ulcerative colitis had been previously diagnosed, had respiratory symptoms and were referred for assessment (table 1). Respiratory function tests included forced expired volume in one second (FEV_1) vital capacity (VC), peak expiratory flow rates (PEFR), total lung capacity (TLC), and gas transfer factor for carbon monoxide (TLCO). In every patient a posterior-anterior and left lateral chest radiograph were also obtained. Autoantibodies and rheumatoid factor were determined, as well as precipitin tests for avian and aspergillus antigens. A peripheral blood film and sputum were inspected for eosinophils. In four patients (patients 3, 4, 9 and 10, table 1) fibreoptic bronchoscopy was performed, specimens of bronchial epithelium were taken from the right anterior basal bronchus and fixed in formaldehyde for routine paraffin sections and in glutaraldehyde for thin (1μm) plastic sections which were stained with toluidine blue. In one patient (patient 9, table 2) a specimen was also obtained from a raised bronchial mucosal lesion in the left main bronchus. Eight patients were treated with beclomethasone diproprionate by aerosol 100 μg four times a day; two of these patients received prednisolone 40 mg per day initially, followed by beclomethasone diproprionate (table 2).

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Results

All patients had undergone rectal biopsy and sigmoidoscopy after the onset of bloody diarrhoea, as well as barium enema studies. The histology of all the rectal lesions was consistent with a diagnosis of ulcerative colitis. In three patients no abnormality was demonstrable in the colon with a barium enema and three other patients required colectomy or hemicolectomy to control the disease (table 1). No patient described either a clinically noteworthy previous respiratory illness or any history of atopic disorder.

The presenting respiratory symptom in every

Table 1 *Clinical features of 10 patients including duration and clinical extent of ulcerative colitis, history of sulphasalazine therapy and presenting respiratory symptoms. Asterisk indicates patients from whom bronchial biopsies were obtained.*

Patient		*Sex*	*Age (yr)*	*Duration of ulcerative colitis (yr)*	*Clinical extent of disease*	*Sulphasalazine therapy*	*Duration and presenting respiratory symptoms*
1	FD	F	72	12	Proctitis, normal Ba enema	None for 4 yr	2 yr cough and progressing exercise dyspnoea (grade 3 MRC)[12]
2	DM	F	55	12	Proctitis, extensive colitis	1gm qds	5 yr progressing productive cough and exercise dyspnoea (grade 3 MRC)[12]
3	*ID	M	42	10	Proctitis, normal Ba enema	1gm qds	1 yr progressing cough and exercise dyspnoea (grade 3 MRC)[12]
4	*IR	F	53	2	Proctitis, sigmoid colitis	None for 1 yr	8 months progressing productive cough and exercise dyspnoea (grade 3 MRC)[12]
5	AM	F	70	22	Proctitis, sigmoid colitis	None for 5 yr	8 yr intermittent productive cough
6	MP	F	32	7	Proctocolectomy 5 yr ago	None for 5 yr	4 yr intermittent productive cough
7	MG	F	45	10	Colectomy, ileorectal anastomosis 3 yr ago	None for 3 yr	18 months progressive productive cough
8	TL	M	54	6	Hemicolectomy 2 yr ago	None for 2 yr	1 yr progressive productive cough
9	*MP	F	57	29	Proctitis, normal Ba enema	Never received	29 yr intermittent productive cough
10	*RH	M	47	5	Proctitis, sigmoid colitis	1gm qds	6 yr intermittent productive cough and wheezing

Table 2 *Clinical investigations of the patients, chest radiographs, respiratory function (expressed as a percentage of predicted), smoking history, and response to steroid therapy. Asterisks indicate patients from whom bronchial biopsies were obtained. P = prednisolone, BDP = beclomethasone diproprionate.*

Patient		*Sex*	*Age (yr)*	*Chest radiograph*	*FEV_1 (% predicted)*	*VC (% predicted)*	*PEFR (% predicted)*	*T_{LCO} (% predicted)*	*TLC (% predicted)*	*Blood eosinophils (% predicted)*	*Auto-antibodies*	*Smoking history*	*Symptomatic response with steroid either P and BDP*
1	FD	F	72	Bilateral nodular shadows	89	78	103	54	83	—	—	Nil	Not tried
2	DM	F	55	Bilateral Basal shadows	58	82	28	57	76	—	ANF (+ - +)	Nil	P and BDP unsuccessful
3	*ID	M	42	Bilateral apical shadows	60	70	74	68	70	54	—	Nil	P successful BDP unsuccessful
4	*IR	F	53	Bilateral basal shadows (Bronchiectasis)	33	57	40	60	50	—	—	Nil	BDP successful
5	AM	F	70	Clear	81	120	84	126	120	—	—	Nil	BDP successful
6	MP	F	32	Clear	97	80	99	92	98	—	—	Nil	BDP successful
7	MG	F	45	Clear	134	132	117	114	125	—	—	Ex-14yr	BDP successful
8	TL	M	54	Clear	82	118	88	120	120	—	—	Nil	BDP successful
9	*MP	F	57	Clear	108	108	115	78	92	—	—	Nil	BDP successful
10	*RH	M	47	Clear	72	108	94	76	91	15	—	Ex-8yr	BDP successful

patient was a persistent cough. In nine patients sputum production was also a major feature, but was not usually purulent as judged by microscopy. Four patients developed marked exertional dyspnoea (grade 3 on the Medical Research Council scale). Eight patients had never smoked, but two were longstanding ex-smokers. There was no correlation between the onset of symptoms and the start of sulphasalazine therapy. In six patients the respiratory symptoms developed during periods without treatment and in three of these patients the symptoms began after colectomy. One patient clearly described intermittent exacerbations of respiratory symptoms alternating with episodes of diarrhoea. Respiratory symptoms in two patients progressed despite cessation of sulphasalazine for periods of nine and five months respectively (patients 2 and 3, table 1). Four patients had bilateral shadows on the chest radiograph, basal in three in a pattern suggesting early fibrosing alveolitis, and apical in the fourth. Bronchography was performed in one (patient 4) who, though denying respiratory symptoms until eight months previously, had severe bilateral bronchiectasis. In the six patients who had no exertional dyspnoea, the chest radiograph was normal. Two patients had increased numbers of eosinophils on the peripheral blood film and one of these (patient 3, table 2) had eosinophils in the sputum. One patient had a strongly positive antinuclear factor, but no patient had precipitins to avian or *Aspergillus fumigatus* antigens (table 2). Patient 10 was the only one who had positive responses to common allergens on prick testing.

The respiratory function tests showed normal function in three patients and in the four patients with pulmonary shadows on chest radiography there was a mild to moderate reduction in spirometric lung volumes and TLC together with a reduction in gas transfer factor (TLCO), suggesting principally a restrictive ventilatory defect together with evidence of airflow obstruction in patients 2, 3 and 4. The remaining three patients (patients 5, 8, and 10) had evidence of a minor obstructive defect (table 2).

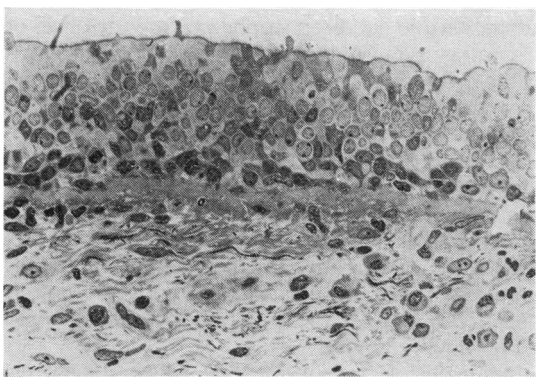

Fig 1 *Bronchial epithelium sections from a patient with ulcerative colitis showing proliferation of reserve cell layer and inflammatory cells in the underlying connective tissue. Epon section, original magnification* $\times 400$.

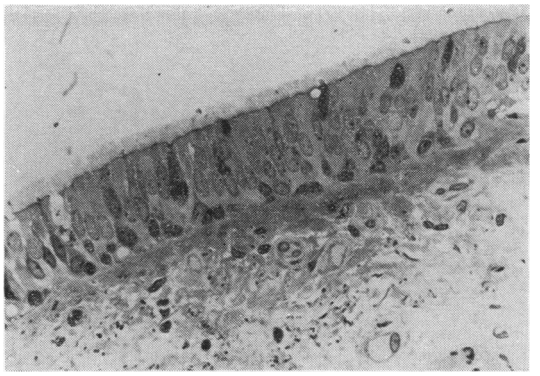

Fig 2 *Bronchial epithelium section from a normal mild smoker (four cigarettes per day). Epon section, original magnification* $\times 400$.

In three patients with radiographic shadows (patients 2, 3, and 4) inhaled beclomethasone diproprionate produced no relief of symptoms. Prednisolone (30 mg per day) restored lung function to normal values in one of these patients (patient 3), clearing the pulmonary shadows as well as abolishing symptoms. But in the other patient (patient 2) in whom both prednisolone and beclomethasone diproprionate were tried both lung function and respiratory symptoms continued to deteriorate. Of the remaining seven patients, the productive cough was immediately abolished by inhaled beclomethasone diproprionate treatment but airflow obstruction was not improved over a period of six months.

In bronchial epithelial biopsies from two patients with clear lung fields and two with pulmonary shadows, changes were most readily observed on light microscopy using 1 μm plastic-embedded sections (fig 1). These consisted of basement membrane thickening, reserve cell hyperplasia, thickening of the epithelium, and infiltration of underlying connective tissue by inflammatory cells. By way of contrast, epithelium is shown in figs 2 and 3, obtained from a light cigarette smoker (five cigarettes per day) and a heavy smoker (30 cigarettes per day). The bronchial mucosal lesion from patient 9 showed partially denuded epithelium with aggregations of mixed inflammatory cells below the basement membrane (fig 4).

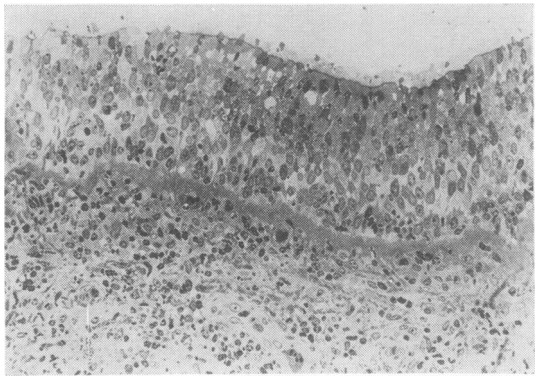

Fig 3 *Bronchial epithelium section from a heavy smoker showing marked reserve cell proliferation and numerous inflammatory cells extending from the underlying connective tissue into the overlying epithelium. Epon section, original magnification* $\times 250$.

Discussion

Pulmonary disease in association with ulcerative colitis may range from alveolitis to bronchitis,[1-5] and we report 10 patients with ulcerative colitis presenting with such a range of pulmonary diseases. Biopsies from all four (two with bronchitis and two with physiological evidence of a restrictive ventilatory defect) showed changes in the bronchial epithelium, consisting of basal cell hyperplasia, basement membrane thickening, submucosal inflammation, and an overall increase in thickness of the epithelium. Changes such as these are usually associated with cigarette smoking,[6] presumably a response to chronic irritation. As our patients were all non-smokers or long-term ex-smokers and direct questioning failed to identify any other potential inhaled irritants, it seems likely that these changes represent a real association with ulcerative colitis.

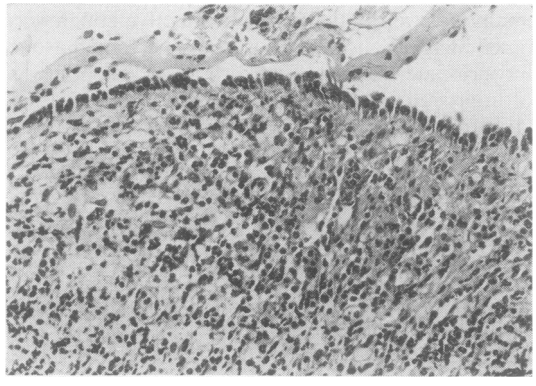

Fig 4 *Ulcerated bronchial epithelium from patient 9 with ulcerative colitis showing loosely attached fibrinous membrane and residual reserve cell layer. The connective tissue below is extensively infiltrated by inflammatory cells. Epon section, original magnification* $\times 250$.

There are some similarities, morphological and developmental, between colonic and bronchial epithelium. Both are derived from primitive gut, the lungs arising from the laryngo-tracheal bud. Both are columnar epithelia with globlet cells and submucosal mucous glands. The non-specific inflammatory changes beneath the bronchial epithelium are similar to those seen beneath colonic epithelium in ulcerative colitis.[7] It is possible, therefore, that a systemic factor, as yet undefined, is responsible for the common response at both epithelial sites in patients with ulcerative colitis. Alternatively, both bronchial and colonic epithelium may be unduly sensitive to contact with common irritants, which are inhaled into the bronchi and also ingested. The non-specific epithelial changes may thus reflect a heightened responsiveness to such hypothetical irritants.

The association between inflammatory bowel disease and lungs is not surprising. Other conditions such as Behçet's and Crohn's disease may affect mouth and colon,[8 9] and Crohn's disease has been reported to involve the larynx.[10] One undoubted cause of pulmonary disease in ulcerative colitis, confirmed by challenge testing, is an idiosyncratic response to sulphasalazine, resulting in both airways and alveolar reactions[1 2 11] sometimes associated with eosinophilia. More recently a purely bronchial disease has been described[5] similar to that seen in six of our patients in whom sulphasalazine therapy could not be incriminated. In only two of our patients was the purely alveolitic picture seen (patients 1 and 3), and in both the fact that sulphasalazine had been stopped before the onset of respiratory symptoms had not affected the progress of the condition. The remaining patients had many "bronchial" features, such as a productive cough, airflow obstruction and, in patient 4, bronchiectasis. In only one of these patients was there any temporal relationship between the onset of symptoms and sulphasalazine therapy. In three patients the symptoms began after colectomies had been performed. Furthermore topical steroids relieved symptoms in seven patients, supporting the notion that airway epithelial changes were responsible for the productive cough.

In conclusion, we suggest that there is an association between ulcerative colitis and lung disease in which patients have chronic cough and show hyperplastic and inflammatory changes in their bronchial mucosa. The predominant clinical picture appears

more commonly to be a bronchial disease rather than the alveolitis which has previously been described as a reaction to sulphasalazine. Inhaled beclomethasone diproprionate by aerosol appeared to provide satisfactory therapy for the symptoms of this condition.

We are grateful to Dr P Forgacs for permission to study three of his patients.

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